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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,362	10/31/2003	Ivan Svendsen	6600.200-US	3030

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,362	SVENDSEN ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 30-33* is/are pending in the application.

4a) Of the above claim(s) *17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response received October 19, 2005 is acknowledged.

Claims 1, 2, 30, and 32 have been amended.

Claims 18-29 have been canceled.

Claims 1-17 and 30-33 are pending.

Applicant's election of Group I, claims 1-16 and 30-33, drawn to anti-TF antibodies and cells that produce said antibodies, in the reply filed on October 19, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 17 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse as explained above in the reply filed on October 19, 2005.

Claims 1-16 and 30-33 are under examination as they read on anti-TF antibodies and cells that make anti-TF antibodies.

Information Disclosure Statement

2. Applicant's IDS received January 29, 2004 is acknowledged and has been considered.

Specification

3. Applicant is thanked for the amendments to the specification to insert SEQ ID numbers where appropriate.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

4. Claims 1 and 4-7 are objected to because the base claim recites "antibody" while the dependent claims recite specific fragments of an antibody molecule. It is noted that the specification on page 6 defines the term antibody to include whole antibody molecules as well as fragments of antibody molecules. Therefore, in the interest of clarifying the scope of the instant claimed products, applicant is invited to consider amending the claims to recite, for example, "An isolated humanized antibody or fragment thereof that ..."

Claims 13 and 14 are objected to because while they specify that particular amino acids must be contained with the epitope bound by the claimed antibodies, the specification does not appear to contain the complete sequence of human tissue factor

(TF). Since the claims recite specific residues of TF, it appears that the sequence of human TF is essential subject material that should be contained within the disclosure of the instant invention. It is suggested that applicant consider amending the specification to incorporate the sequence of human TF if basis for such incorporation, such as via incorporation by reference, can be found within the specification so as not to introduce new matter. Applicant is reminded that essential material cannot be incorporated from foreign patents, foreign patent applications, or non-patent literature. See MPEP 608.01(p).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 13, 16, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, recitation of "the epitope" in line 3 of claim 12 renders the claim and its dependent claims indefinite because it is unclear if "the epitope" is the epitope identified in claim 1 or is the second epitope identified in claim 11. The "epitope" recited in line 6 of claim 33 is also subject to a similar alternate interpretations concerning which epitope is being further limited. Additionally, it is not clear from the comprising language of claim 12 if the two epitopes must minimally have at least one amino acid in common, have a smaller epitope sequence completely contained within a larger epitope sequence, or if the two epitopes

are of exactly the same size and sequence, thus making them a single epitope. Appropriate clarification is required, with possible use of terms such as first epitope and second epitope, if such language is supported in the specification, and more precise language describing the structural sequence relationship between the epitopes being a possible way to increase the clarity of the claimed subject matter and thus obviate this rejection.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies that bind to TF with an affinity of about 10^{-10} M or less, does not reasonably provide enablement for antibodies that bind with affinities of between about 10^{-10} and 10^{-15} M. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has claimed humanized antibodies that bind human tissue factor with affinities in the range of 10^{-8} to 10^{-15} M. The specification does not appear to teach any working examples of humanized antibodies. It is known that higher affinity antibodies can be generated *in vivo* by the process of somatic hypermutation during a recall

response, but such antibodies rarely exceed an affinity of 10^{-10} M (Janeway et al., Immunobiology, Third edition, 1997, pages 9:42-9:43, see entire selection, particularly Figure 9:34). Standard methods used in the art for humanizing antibodies generate antibodies that have affinities that are either the same or are slightly reduced as compared to the starting nonhuman antibody (Queen et al., US Patent 5,693,762, see entire document, particularly lines 33-43 of column 3 and lines 54 to 67 of column 10). It was also known in that art that high affinity antibodies could be produced using phage display technologies (Hanes et al., Nature Biotechnology, 2000, 18:1287-1292 and Lee et al., J. Mol. Biol., 2004, 340:1073-1093, see entire documents). However, even using phage display technologies, the recovered antibodies did not bind more strongly than about $2x10^{-11}$ M (see particularly Table 1 and the last sentence of the first paragraph of the Conclusions section of Hanes et al. and Figure 4 of Lee et al.). The techniques that allowed for generation of antibodies with affinities up to 10^{-11} M incorporated extensive mutagenesis, particularly in the CDR sequences. As taught by Janeway et al., the CDR sequences (also known as hypervariable sequences, 3 of which are located on the antibody heavy chain and 3 on the antibody light chain) are predominantly responsible for epitope binding and specificity (Janeway et al, see pages 3:7-3:9, particularly section 3-6). It is particularly noteworthy that applicant's prophetic Example 7 does not appear to allow for changes to the CDR sequences isolated from the parent mouse monoclonal antibody).

Therefore, given that antibodies with binding affinities greater than 10^{-10} M are not normally generated in nature, that even when using artificial screening and selection

technologies incorporating phage display technologies recovered antibodies have not been shown to have binding affinities greater than about 10^{-11}, the fact that the technologies used to achieve such strong binding allow for CDR mutations that do not seem to be permitted based upon applicant's teachings for how to make a humanized antibody, and the fact that applicant has not demonstrated that the disclosed method does generate antibodies that have affinities of up to 100000X stronger than what is typically achieved during somatic hypermuation *in vivo*, it is reasonable that a skilled artisan would not be able to make or use antibodies covering the full scope of the recited affinity ranges without conducting additional research.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-4, 6-9, 11, 12, 15, 16, and 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. (US Patent No. 5,986,065, see entire document).

Wong et al. teach multiple mouse monoclonal antibodies such as I43, K80, L102 and L133 that bind human tissue factor (TF) and inhibit the binding of FVIIa to TF (see entire document, particularly the abstract and Figure 4). The antibodies disclosed by Wong et al. also have affinities of at least about $1x10^{-10}$ M (see particularly Figure 2 and lines 52-64 of column 4). Human and humanized antibodies, as well as their methods of production are also disclosed (see particularly from line 46 of column 8 to line 5 of column 9), with the mammalian cell line X63-Ag8.653 being taught as particularly useful for antibody production (see particularly lines 45-55 of column 13). Antibody fragments such as F(ab), $F(ab')_2$, and single chain Fv are also taught (see particularly lines 41-58 of column 9). The antibodies of Wong et al. are also taught for use as part of a pharmaceutically acceptable composition (see particularly from line 63 of column 9 to line 62 of column 10). Given the ambiguity discussed above concerning epitopes and second epitopes of TF, and the reasonable interpretation that they can be the same epitope, claims 11, 12, 16, and 33 have been included in this rejection because they do teach an epitope of TF bound by an antibody. Further, it appears that the recitation in claim 11 and its dependent claims that the frameworks of the humanized antibody be derived from a human antibody that also binds TF is an attempt to introduce a product by process limitation into the claims. Applicant is reminded that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even

though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). In the instant case it does not appear that a humanized antibody made using the process introduced in claim 11 would generate a product different from a humanized antibody generated using standard art techniques, since in both instances the product will be an antibody comprising human Fc domains and non-human CDR sequences in human framework regions.

Therefore, the prior art anticipates the claimed invention.

10. Claims 1-4, 6-9, 11-16, and 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Kirchhofer et al. (US Patent No. 6,703,494, see entire document).

Kirchhofer et al. teach multiple antibodies that bind to human tissue factor and inhibit the binding of FVIIa (see entire document, particularly the abstract, lines 23-28 of column 35, lines 54-61 of column 36, lines 1-3 of column 38, and lines 64-67 of column 39). The antibodies taught by Kirchhofer et al. are mouse monoclonal antibodies, human antibodies, and humanized antibodies (see particularly from line 15 of column 15 to line 67 of column 19 and Examples 1 and 2). Kirchhofer et al. also disclose that their antibodies can be made into antibody fragments such as F(ab), $F(ab')_2$, and single chain Fv molecules, and that antibodies of their invention can be used in pharmaceutical compositions (see particularly lines 52-57 of column 13, from line 1 of column 20 to line 42 of column 21, and from line 63 of column 26 to line 3 of column 28). Cell lines taught as being useful for the production of the antibodies of Kirchhofer et al. include the mammalian cell lines Sp-2, X63-Ag8-653, and CHO (see particularly

lines 1-48 of column 16). Binding affinities for some of the disclosed antibodies were measured, with antibody 7G11 in particular having a K_d of greater than $1x10^{-10}$ M (see particularly Table 2 in column 36). Epitope mapping experiments were also conducted by Kirchhofer et al., and they discovered that the epitope bound by 7G11 comprises Lys46 of human TF, while the epitopes bound by 6B4 and HTF1 comprise Try94 of human TF (see particularly lines 19-30 of column 37 and Figure 5). Note that the epitopes bound by antibodies 6B4 and HTF1 are similar, but are not the same (see particularly lines 25-30 and 54-56 of column 37 and Figure 5).

In claim 11 and its dependent claims, it appears that the recitation that the frameworks of the humanized antibody be derived from a human antibody that also binds TF is an attempt to introduce a product by process limitation into the claims. Applicant is reminded that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). In the instant case it does not appear that humanized antibody made using the process introduced in claim 11 would generate a product different from a humanized antibody generated using standard art techniques, since in both instances the product will be an antibody comprising human Fc domains and non-human CDR sequences in human framework regions.

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent No. 5,986,065, see entire document) in view of Carney (US Patent 5,081,230, see entire document).

The teachings of Wong et al. have been discussed above. These teachings differ from the claimed invention in that they do not teach the antibody fragment $F(ab)_2$.

Carney teaches methods of making antibody fragments such as $F(ab)_2$, and teaches that and advantage enjoyed by $F(ab)_2$ fragments as compared to whole antibodies is that they have less nonspecific background activity and are less immunogenic *in vivo* (see entire document, particularly lines 1-20 of column 9).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to make $F(ab)_2$ fragments from the antibodies taught by Wong et al. in order to gain the advantages of reduces nonspecific activity and reduced immunogenicity when administered *in vivo*.

13. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchhofer et al. (US Patent No. 6,703,494, see entire document) in view of Carney (US Patent 5,081,230, see entire document).

The teachings of Kirchhofer et al. have been discussed above. These teachings differ from the claimed invention in that they do not teach the antibody fragment $F(ab)_2$.

Carney teaches methods of making antibody fragments such as $F(ab)_2$, and teaches that and advantage enjoyed by $F(ab)_2$ fragments as compared to whole antibodies is that they have less nonspecific background activity and are less immunogenic *in vivo* (see entire document, particularly lines 1-20 of column 9).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to make $F(ab)_2$ fragments from the antibodies taught by Kirchhofer et al. in order to gain the advantages of reduces nonspecific activity and reduced immunogenicity when administered *in vivo*.

14. Claims 1-4, 6-9, 11-16, and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al. (US Patent No. 5,223,427, of record on the IDS

received January 29, 2004, see entire document) in view of Queen et al. (US Patent 5,693,762, see entire document).

Edgington et al. teach mouse monoclonal antibodies that specifically bind to human TF and inhibit the binding FVIIa (see entire document, particularly the abstract, Figure 17, Table 8, and lines 3-7 of column 53). Edgington et al. also teach how to make antibody fragments such as F(ab), $F(ab')_2$, and single chain Fv molecules, and the use of antibodies and fragments of antibodies in pharmaceutical preparations (see particularly from line 30 of column 20 to line 65 of column 21). A specific disclosed use for the antibodies of Edgington et al. is to modulate the binding of FVIIa to TF *in vivo* (see particularly from line 35 of column 22 to line 17 of column 24). Epitope mapping studies were conducted, and many antibodies bound non-identical epitopes comprising residues Trp45, Lys46, and Try94 of human TF (see particularly Table 5). These teachings differ from the claimed invention in that Edgington et al. do not teach how to make humanized antibodies and they did not measure the binding affinities of their antibodies.

Queen et al. teaches methods of humanizing mouse monoclonal antibodies (see entire document, particularly the abstract). Administration of nonhuman antibodies to human patients is known to generate unwanted immune responses (such as the HAMA response) due to the immunogenicity of the administered antibody, and humanization offers the advantage of reducing the immunogenicity, increasing the effector function, and increasing the half-life of the administered antibody (see particularly lines 6-27 of column 16). Queen et al. also teach that the affinities of humanized antibodies are at

least about $1x10^{-8}$ M and are preferably at lest about $1x10^{-10}$ M (see particularly lines 57-61 of column 10). Methods for making humanized antibody fragments including F(ab), $F(ab')_2$ and single chain Fv molecules are also disclosed (see particularly lines 17-34 of column 11).

Therefore it would have been obvious to a person of ordinary skill in the art to make a humanized antibody from the antibodies taught by Edgington et al. Motivation to do so comes from the teachings of Edgington et al. that their antibodies are to be used for *in vivo* methods of treatment, and the teachings of Queen et al. that humanized antibodies offer the advantages of reduced immunogenicity, increased effector function and increased half-life when administered to patients.

In claim 11 and its dependent claims, it appears that the recitation that the frameworks of the humanized antibody be derived from a human antibody that also binds TF is an attempt to introduce a product by process limitation into the claims. Applicant is reminded that "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). In the instant case it does not appear that humanized antibody made using the process introduced in claim 11 would generate a product different from a humanized antibody generated using the methods of Queen et al. using the antibodies of Edgington et al. as

the starting material, since in both instances the product will be an antibody comprising human Fc domains and non-human CDR sequences in human framework regions.

15. No claims are allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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December 14, 2005

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12/23/05